Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial*

Jens U. Jensen, MD, PhD; Lars Hein, MD; Bettina Lundgren, MD, DMSc; Morten H. Bestle, MD, PhD; Thomas T. Mohr, MD, PhD; Mads H. Andersen, MD; Klaus J. Thornberg, MD; Jesper Løken, MD; Morten Steensen, MD; Zoe Fox, MD, PhD; Hamid Tousi, MD; Peter Søe-Jensen, MD; Anne Ø. Lauritsen, MD; Ditte Strange, MD; Pernille L. Petersen, MD; Nanna Reiter, MD; Søren Hestad, MD; Katrin Thormar, MD; Paul Fjeldborg, MD; Kim M. Larsen, MD; Niels E. Drenck, MD; Christian Østergaard, MD, PhD, DMSc; Jesper Kjær, MSc; Jesper Grarup, DVM; Jens D. Lundgren, MD, DMSc; for The Procalcitonin And Survival Study (PASS) Group

Objective: **For patients in intensive care units, sepsis is a common and potentially deadly complication and prompt initiation of appropriate antimicrobial therapy improves prognosis. The objective of this trial was to determine whether a strategy of antimicrobial spectrum escalation, guided by daily measurements of the biomarker procalcitonin, could reduce the time to appropriate therapy, thus improving survival.**

Design: **Randomized controlled open-label trial.**

Setting: **Nine multidisciplinary intensive care units across Denmark.**

Patients: **A total of 1,200 critically ill patients were included after meeting the following eligibility requirements: expected intensive care unit stay of ≥24 hrs, nonpregnant, judged to not be harmed by blood sampling, bilirubin <40 mg/dL, and triglycerides <1000 mg/dL (not suspensive).**

Interventions: **Patients were randomized either to the "standard-of-care-only arm," receiving treatment according to the current international guidelines and blinded to procalcitonin levels, or to the "procalcitonin arm," in which current guidelines were supplemented with a drug-escalation algorithm and intensified diagnostics based on daily procalcitonin measurements.**

Measurements and Main Results: **The primary end point was death from any cause at day 28; this occurred for 31.5% (190 of 604) patients in the procalcitonin arm and for 32.0% (191 of 596) patients in the standard-of-care-only arm (absolute risk reduction, 0.6%; 95% confidence interval [CI] −4.7% to 5.9%). Length of stay in the intensive care unit was increased by one day (p = .004) in the procalcitonin arm, the rate of mechanical ventilation per day in the intensive care unit increased 4.9% (95% CI, 3.0–6.7%), and the relative risk of days with estimated glomerular filtration rate <60 mL/min/1.73 m^2 was 1.21 (95% CI, 1.15–1.27).**

Conclusions: **Procalcitonin-guided antimicrobial escalation in the intensive care unit did not improve survival and did lead to organ-related harm and prolonged admission to the intensive care unit. The procalcitonin strategy like the one used in this trial cannot be recommended. (Crit Care Med 2011; 39:2048–2058)**

KEY WORDS: antibiotics; bacterial infection; biomarker guidance; mortality; procalcitonin; sepsis

Sepsis, pneumonia, and meningitis are examples of infectious conditions that continue to have a high mortality rate in intensive care units in Europe and North America (1–3). Clinicians in intensive care units have recognized that an organized and systematic approach to delivering interventions with proven efficacy is important, as emphasized in the Surviving Sepsis Campaign, and that prompt institution of appropriate therapy, defined as delivering an antibiotic active against the identified causative process within a few hours of syndrome recogni-

***See also p. 2182.**

From the Copenhagen HIV Programme (JUJ, ZF, JK, JG, JDL), University of Copenhagen, Copenhagen, Denmark; the Departments of Clinical Microbiology (JUJ, BL) and Anaesthesia and Intensive Care (JL, MS), Copenhagen University Hospital, Hvidovre, Denmark; the Department of Anaesthesia and Intensive Care (LH, AØL, DS, PLP), Copenhagen University Hospital, Glostrup, Denmark; the Department of Anaesthesia and Intensive Care (LH, MHB, SH), Copenhagen University Hospital, Hillerød, Denmark; the Department of Anaesthesia and Intensive Care (TTM, KJT, KT), Copenhagen University Hospital, Gentofte, Denmark; the Department of Anaesthesia and Intensive Care (MHA, PF), Aarhus University Hospital, Skejby, Denmark; Royal Free Hospital (ZF), University College London, London, UK; the Departments of Anaesthesia and Intensive Care (HT, PSJ) and Clinical Microbiology (CØ), Copenhagen University Hospital, Herlev, Denmark; the Department of Anaesthesia and Intensive Care (NED, NR), Copenhagen University Hospital, Roskilde, Denmark; the Department of Anaesthesia and Intensive Care (KML), Aarhus University Hospital, Aarhus, Denmark; and the Department of Infectious Diseases (JDL), Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

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For information regarding this article, E-mail: juj@cphiv.dk

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tion, is one of the most effective interventions for improving prognosis in the intensive care setting (4–6).

Clinician judgment is pivotal to choosing the right drug or combination of drugs for initial therapy of sepsis or other acute infections in the intensive care unit. Given the plethora of community- and hospital-acquired pathogens, and the increasing incidence of antimicrobial resistance, there is more risk that empiric therapy will fail to cover the causative pathogen (7).

If a laboratory marker could be identified that would provide an early warning that antimicrobial therapy was inappropriate, patient outcome might be improved. Procalcitonin, a fast-reacting biomarker of bacterial infection (8), has been proposed as a tool to obtain this goal (9). Initial reports, summarized in a study by Uzzan et al (10), reported good performance in critically ill patients; however, more recent reports have observed a low performance of procalcitonin in this setting (11–13). Several trials have been conducted with the aim to use different procalcitonin strategies in antibiotic stewardship to reduce the use of antimicrobials in intensive care units and emergency departments (14–17).

The primary aim of the study was to determine whether the prompt availability of procalcitonin levels and a corresponding, obligatory guideline for antimicrobial interventions would result in initiation of appropriate antimicrobial therapy earlier in infected critically ill patients and thus improve 28-day survival compared with standard clinical judgment unenhanced by available procalcitonin levels. Secondary aims were to determine whether the procalcitonin-guided strategy would lead to a shorter duration of organ failure or a shorter stay in the intensive care unit. Prespecified subgroup analyses were performed using the following seven subgroup separators: age (≥65 vs. <65 yrs), gender, Acute Physiology and Chronic Health Evaluation score (≥20 vs. <20), site of recruitment, degree of infection (severe sepsis/septic shock vs. milder or no infection as defined [18, 19]), date of recruitment (before vs. after January 1, 2008), and whether surgery had been performed in the 24 hrs before enrollment. We investigated this in a randomized trial, called the Procalcitonin And Survival Study (PASS), in Denmark.

MATERIALS AND METHODS

PASS is a randomized controlled trial conducted at mixed medical/surgical intensive care units in nine regional tertiary care public university hospitals in Denmark in 2006–2009.

Patients. To be eligible, patients had to be ≥18 yrs of age, enrolled within 24 hrs of admission to the intensive care unit, and have an expected intensive care admission length of ≥24 hrs. Patients with known highly elevated bilirubin levels (>40 mg/dL) or triglycerides (>1000 mg/dL) were not eligible (interference with procalcitonin measurements). Additionally, patients who were judged to be at an increased risk from blood sampling were not eligible. The inclusion criteria were broad because infection is frequent and often causes complications in the patient group and to increase the external validity of the results. The person or next of kin gave informed consent. The study protocol was approved by the regional ethics committees in Denmark (H-KF-272-753) and adheres to the Helsinki declaration revised in Seoul in 2008.

Procalcitonin Measurements. Samples were made straight after inclusion and thereafter everyday between 3:00 AM and 6:00 AM and subsequently collected at the intensive care unit by a courier who transported them to the central laboratory. They had to arrive before 8:00 AM and they were cooled during transport. An analysis run with the used equipment was approximately 1 hr, including centrifugation, analysis, maintenance, and result printing. The results were then entered into the database and the aim was to present results before 11:00 AM each day 7 days/wk throughout the year. The project coordinator or a substitute followed up on this everyday and took care of any delay. A back-up laboratory at a collaborating laboratory made the analyses if the equipment broke down. C-reactive protein was measured as part of the standard of care daily in all patients. If the patient sustained cardiac arrest or in another way in an urgent life-threatening condition, all study-related procedures were postponed and were later resumed.

Randomization and Blinding. Randomization was performed 1:1 using a computerized algorithm created by the database manager with concealed block size, prestratified for site of recruitment, initial Acute Physiology and Chronic Health Evaluation, and age (entered in an encrypted screening form in a password-protected Web site); investigators were masked to assignment before randomization. All investigators were trained by the coordinating center and had to register in an investigator database. Investigators, treating physicians, and the coordinator were unaware of outcomes during the study as were all procalcitonin measurements in the standard-of-care-only (control) group.

Interventions and Definitions. In the standard-of-care-only group, the antimicrobial treatment was guided according to current clinical guidelines (5, 20). "Infection" and the different host responses to this were defined as in the study by Levy et al (19). In the procalcitonin group, the use of antimicrobial interventions was guided by the same clinical guidelines as in the standard-of-care-only group and additionally by daily procalcitonin measurements classified as "alert procalcitonin" or "nonalert procalcitonin" with a corresponding obligatory intervention algorithm. The interventional algorithm was available at all sites and all investigators were trained in it. Additionally, everyday, all sites were contacted by telephone (365 days/yr) to assure that interventions were conducted according to the algorithm. The main principle in the intervention algorithm was whenever an "alert procalcitonin" occurred, 1) to substantially increase the antimicrobial spectrum covered and 2) to intensify the diagnostic effort to find uncontrolled sources of infection, in this way interpreting an "alert procalcitonin" as a warning of uncontrolled infection. "Alert procalcitonin" was defined as a procalcitonin ≥1.0 ng/mL that was not decreasing at least 10% from the previous day. At baseline, a single procalcitonin measurement of ≥1.0 ng/mL was considered to be "alert procalcitonin." Both arms received antimicrobial therapy according to current guidelines. Culture samples from blood, urine, airways, and other suspected sites were performed according to the standard of care in both groups at: admission, three times per wk, and whenever infection was suspected. Procalcitonin-guided therapeutic and diagnostic interventions were thus as a concept a new indication to start or escalate antimcrobial therapy in situations in which, according to the hypothesis, uncontrolled infection was developing in a clinical picture not clearly indicating therapy shift. Interventional principles for the procalcitonin group and standard-of-care antimicrobial principles are displayed in Figure 1, and an example of the site-specific interventional algorithm is available in the Supplemental Table S1 (see Supplemental Digital Content 1, http://links.lww.com/CCM/A256).

The choice of standard of care empiric therapy was mainly based on the suspected focus on the infection. The low level of antibiotic resistance in Denmark among important pathogens (e.g., approximately 1% methicillin-resistant *Staphylococcus aureus*, <3% penicillin-resistant pneumococci, approximately 5% cefuroxime-resistant *Escherichia coli*, <1% vancomycin-resistant enterococci) was taken into consideration (21). Based on these principles, the following antimicrobials were used if no specific reason made an alternative choice relevant: 1) urinary tract infection was treated with cefuroxime ± ciprofloxacin; 2) abdominal focus with piperacillin–tazobactam in combination with ciprofloxacin and metronidazole and fluconazole was added after reoperation or fecal peritonitis; 3) community-acquired pneumonia was treated with cefuroxime in combination with ciprofloxacin/

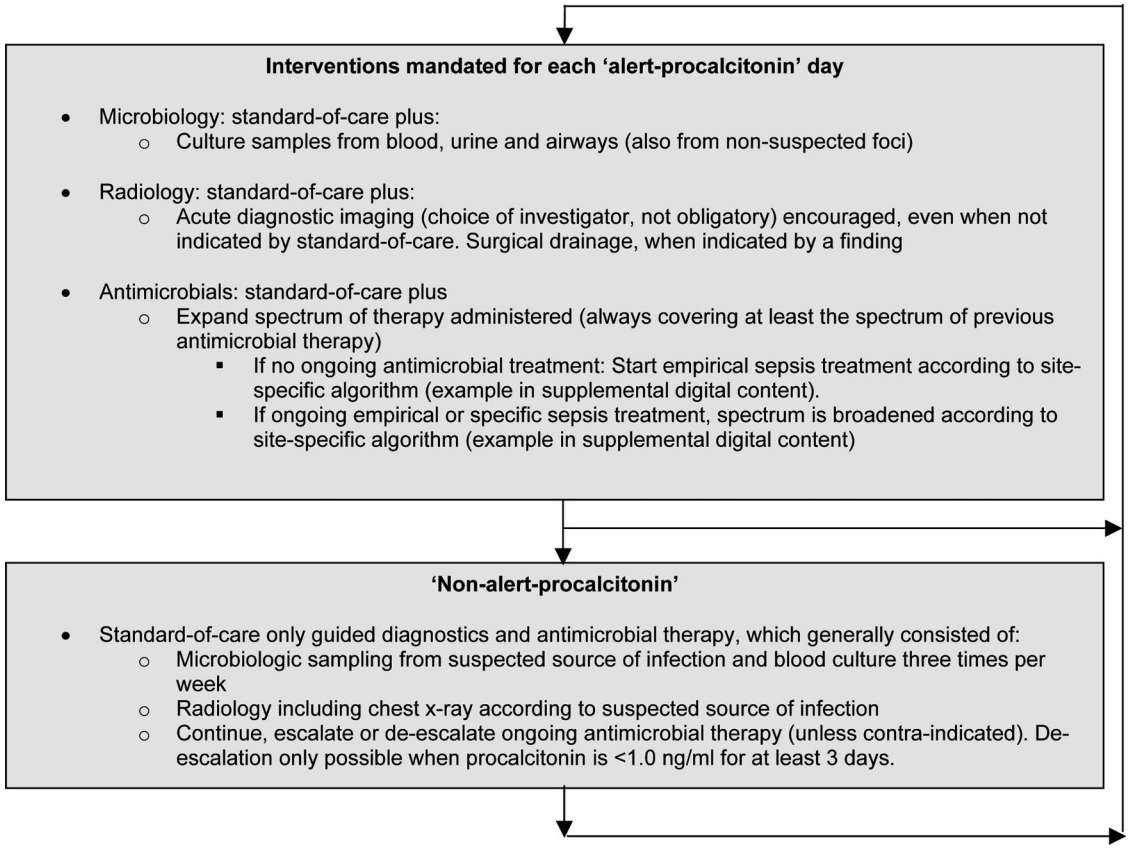

Figure 1. General principles of procalcitonin-guided intervention. At "alert procalcitonin" (≥1.0 ng/mL and not decreasing by at least 10% from the previous day), interventions were obligatorily conducted according to an algorithm with specific instructions for intervention, which was adapted to the antimicrobial guidelines on the site. Antimicrobials were daily adjusted according to: 1) present and previous procalcitonin values; 2) infectious state of the patient (clinical presentation, microbiology, radiology, etc.); and 3) history of antimicrobial use. Procalcitonin-guided antimicrobial escalation was mandatory, except when: 1) there was a clear contraindication for administering it or 2) microbiology "explaining the infectious presentation of the patient" was announced (same date) leading to specific therapy. Standard-of-care antimicrobial diagnostics and treatment were not waived in the procalcitonin arm (nor the standard-of-care-only arm) to assure patient safety. According to the standard-of-care principle, all patients with septic shock were treated at the onset of hypotension with antimicrobials covering >95% of the causes of this condition in our hospitals. Awaiting procalcitonin results/low procalcitonin levels was not considered a plausible reason to withhold antimicrobial treatment. The treating physician was reminded daily by telephone from the coordinating center at each "alert procalcitonin" to intervene. In the standard-of-care arm, procalcitonin measurements were not available.

moxifloxacin or a macrolide; 4) hospital-acquired pneumonia including ventilator-associated pneumonia was treated with piperacillin–tazobactam or a carbapenem and if the result of aspiration combined with metronidazole; 5) vancomycin was added for suspected catheter-related infection; and 6) an unknown focus was treated with piperacillin–tazobactam or a carbapenem in combination with ciprofloxacin and metronidazole. Combination therapy with aminoglycosides was rarely considered as a result of nephrotoxicity.

Procalcitonin samples were made daily in the intensive care unit beginning immediately after randomization and blood analysis was made using the Kryptor-PCT (Brahms Diagnostica, Hennigsdorf, Germany). The functional assay sensitivity is 0.06 ng/mL and procalcitonin is stabile at 4°C for until 96 hrs (22).

Appropriate antimicrobial therapy was considered to be antimicrobials with *in vitro* activity for the isolated pathogen or pathogens.

Data Collection and Follow-Up. Mortality status during follow-up was determined through the National Patient Register. This system is updated every 14 days. The register was accessed 216 days after the last patient was recruited. Other follow-up information was collected using case report forms with daily registrations. Patients discharged from the intensive care unit were assumed to no longer use mechanical ventilation. Good Clinical Practice was applied. As part of this, double-keying, monitoring, and correction of errors and missing data were done in collaboration between the investigator and a clinical monitor.

Statistical Analysis. The primary analysis includes all patients who were randomized. All of the end points were listed in the original protocol and all populations studied, including both the intention-to-treat population and the subgroup analyses, were analyzed according to a prespecified analysis plan.

Comparisons were made between treatment arms using Student's *t* tests and Mann-Whitney *U* tests (continuous data). Chi-squared tests were used to test categorical variables, at small numbers, using Fisher's exact test. Time-to-event analyses were performed using Kaplan-Meier plots and Cox proportional hazards models. Interactions were explored. Statistical analyses were performed using STATA version 10.2 (STATA Corp, College Station, TX), except analyses regarding appropriate antimicrobials, in which SAS version 9.1 (SAS Institute Inc, Cary, NC) was used. All reported *p* values are two-sided using a level of significance of .05. An estimate of the predictive ability of "alert procalcitonin" was tested against the primary end point together with: age (≥65 vs. <65 yrs), Acute Physiology and Chronic Health Evaluation score, degree of infection (severe sepsis/septic shock vs. milder or no infection as defined (19), comorbidity (Charlson's score ≥2 vs. <2), body mass index (≥25 vs. <25 kg/m^2), cancer (present vs. not), glo-

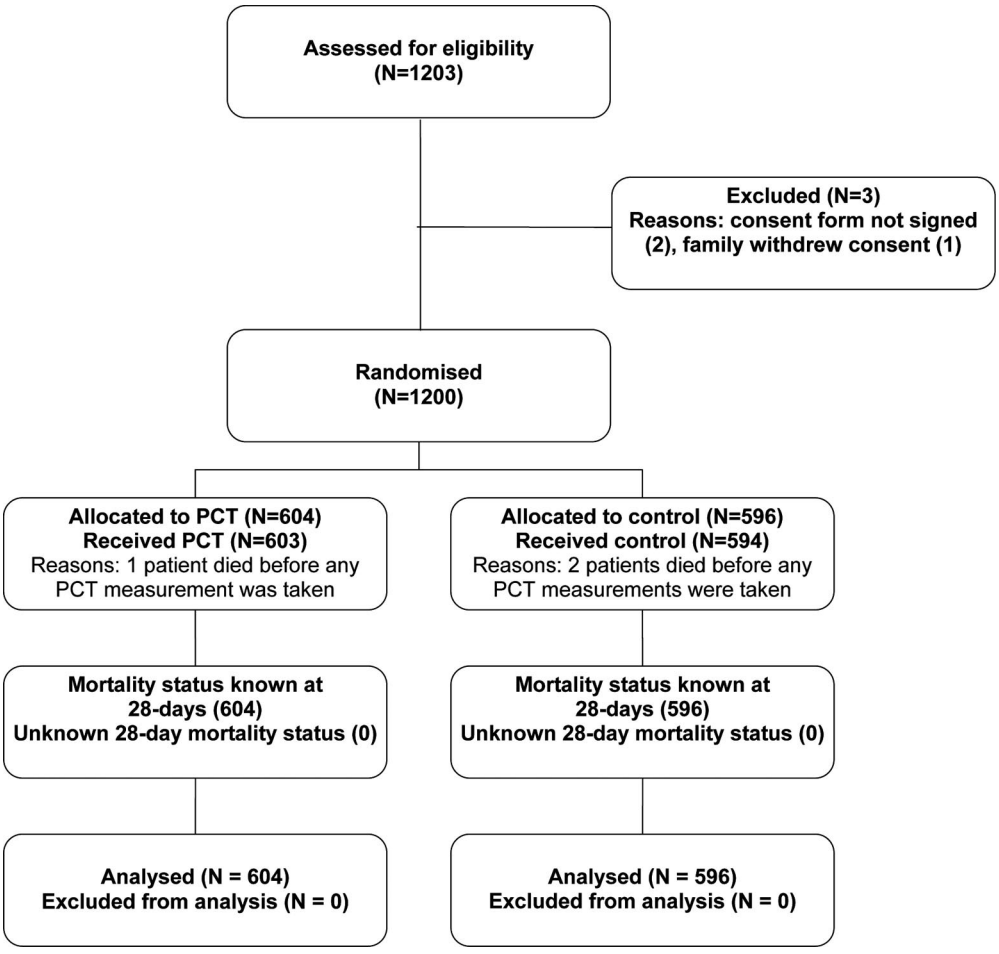

Figure 2. Trial profile. *PCT*, placebo-controlled trial.

merular filtration rate (>60 mL/min/1.73 m^2, 31–60 mL/min/1.73 m^2, ≤30 mL/min/1.73 m^2), and whether surgery had been performed in the 24 hrs before enrollment.

The final (adjusted) sample size of 1200 patients was based on an estimated mortality in the standard-of-care-only group of 31.0% and a proposed absolute risk reduction of 7.5%. These numbers were estimated from a cohort study we performed (23) and studies estimating the importance of timely and appropriate antimicrobials on the mortality in infected critically ill patients (6, 24, 25). O'Brien and Fleming principles were used at interim analysis (26). Detailed sample size considerations are available in the supplemental data (see Supplemental Digital Content 2, http://links.lww.com/CCM/A257).

RESULTS

Baseline Characteristics

Nine sites enrolled 1200 patients between September 1, 2006, and February 6, 2009 (Fig. 2). At baseline (time of randomization), 996 (83%) patients were judged to have "infection," and 975 (81%) patients had chronic comorbidity. Table 1 summarizes baseline characteristics.

Follow-Up

Follow-up for the primary end point was complete (100.0%) for all patients randomized (604 in the procalcitonin group, 596 in the standard-of-care-only group). Follow-up for mechanical ventilation, dialysis, estimated glomerular filtration rate, and use of antibiotics in the intensive care unit was reached in 578 of 604 (95.7%) vs. 559 of 596 (93.8%) (p = .14). Overall, the time followed in the recruiting intensive care unit in the procalcitonin arm was 5,447 of 5,700 days spent in any intensive care unit (95.6%) vs. 4,717 of 5,194 days (90.8%, standard-of-care-only arm). For use of antibiotics in any hospital department, follow-up was 9,866 days of 11,380 admission days (86.7%) vs. 9,348 of 10,755 days (86.9%).

'Alert Procalcitonin' Situations, Prediction of Mortality, and Sensitivity Toward Infection

Procalcitonin results were bioanalyzed and were available in the online system on the day of sampling/according to the protocolized aim for result delivery for 5,174 of 5,447 days (95.0%) vs. 4,416 of 4,717 days (93.6%) (procalcitonin vs. standard-of-care-only) and was unblinded at the same time to the investigators for patients in the procalcitonin group. Less than ten patients had triglycerides or bilirubin levels that interfered with the procalcitonin measurements and in these cases, manual dilution of the sample was used. Five hundred ninety-one patients had "alert procalcitonin" at baseline, 312 (51.7%) in the procalcitonin group and 279 (47.0%) in the standard-of-care-only group, corresponding to a 59.3% sensitivity (591 of 996) patients toward infection/host response. During follow-up, a total of 638 patients (53%) developed a first or recurrent "alert procalcitonin."

Table 1. Baseline characteristics of the study participants

	Standard-of-Care-Only (n = 596)	Procalcitonin-Guided (n = 604)	Overall (n = 1200)
Age, yrs, median (IQR)	67 (58–75)	67 (58–76)	67 (58–76)
Male sex, no. (%)	333 (55.9)	330 (54.6)	663 (55.3)
Body mass index, median kg/m^2 (IQR)	24.7 (22.0–27.8)	25.0 (22.5–28.7)	24.8 (22.2–27.9)
Acute Physiology and Chronic Health Evaluation II score, median (IQR; range, 0–71)	18 (13–24)	18 (13–25)	18 (13–24)
Surgical patient, no. (%)	260 (43.6)	227 (37.6)	487 (40.6)
Chronic comorbidity[a]			
No chronic comorbidities, no. (%)	102 (17.1)	123 (20.4)	225 (18.8)
1 chronic comorbidity, no. (%)	279 (46.8)	257 (42.6)	536 (44.7)
2 chronic comorbidities, no. (%)	173 (29.0)	171 (28.3)	344 (28.7)
≥3 chronic comorbidities, no. (%)	42 (7.1)	53 (8.8)	95 (7.9)
Acute illness/reason for admittance to the intensive care unit			
Central nervous system incl. unconsciousness	78 (13.1)	101 (16.7)	179 (14.9)
Respiratory failure, no. (%)	422 (70.8)	410 (67.9)	832 (69.3)
Circulatory failure, no. (%)	263 (44.1)	257 (42.6)	520 (43.3)
Gastrointestinal disease, no. (%)	128 (21.5)	96 (15.9)	224 (18.7)
Renal disease, no. (%)	81 (13.6)	103 (17.1)	184 (15.3)
Postoperative complications, no. (%)	123 (20.6)	106 (17.6)	229 (19.1)
Trauma, no. (%)	113 (19.0)	106 (17.6)	219 (18.3)
Other, no. (%)	68 (11.4)	57 (9.4)	125 (10.4)
Indicators of severity			
Temperature, °C, median (IQR; n = 1136)	37.3 (36.3–38.1)	37.4 (36.4–38.3)	37.3 (36.3–38.2)
Mean arterial pressure, mm Hg, median (IQR; n = 1195)	71 (60–84)	72 (63–85)	71 (62–84)
Need for vasopressor/inotropic drug,[b] no. (%; n = 1200)	315 (52.9)	326 (53.4)	641 (53.4)
pH, median (IQR; n = 1185)	7.29 (7.21–7.39)	7.29 (7.20–7.38)	7.29 (7.20–7.38)
Mechanical ventilation used, no. (%; n = 1200)	401 (67.3%)	401 (66.4%)	802 (66.8%)
Creatinine μmol/L, median (IQR; n = 1167)	119 (78–197)	119 (75–208)	119 (76–202)
Dialysis required, no. (%; n = 1200)	88 (14.8%)	86 (14.2%)	174 (14.5)
Infection, clinical assessment[c]			
No infection, no. (%)	118 (19.8)	86 (14.2)	204 (17.0)
Infection without meeting criteria for severe sepsis/septic shock, no. (%)	266 (44.6)	271 (44.9)	537 (44.8)
Severe sepsis/septic shock, no. (%)	212 (35.6)	247 (40.9)	459 (38.3)
Biomarkers			
Alert procalcitonin,[d] no. (%)	279 (47.0)	312 (51.7)	591 (49.4)
Leukocytes × 10^9, median (IQR)	13.0 (8.8–18.1)	12.4 (8.0–18.1)	12.8 (8.4–18.1)
C-reactive protein, mg/L, median (IQR)	152 (54–266)	161 (56–271)	157 (56–271)

IQR, interquartile range.

[a]Chronic comorbidity: earlier diagnosed by hospital admission: heart failure, lung disease, cancer, diabetes, alcohol abuse, chronic infection, neurologic disease, renal diseases, liver disease, gastrointestinal disease, autoimmune disease, cancer, and psychiatric disorders. Acute illness: persons can have several. "Other" includes liver disease, hemorrhage, hematologic disease and poisoning; [b]vasopressors/inotropic drugs are considered to be epinephrine, norepinephrine, dopamine, and dobutamine; [c]infections were rated according to the American College of Chest Physicians/Society of Critical Care Medicine definitions; investigators were trained in using them; [d]alert procalcitonin: procalcitonin level not decreasing by at least 10% from the previous day and >1.0 ng/mL. If only one measurement is available: absolute procalcitonin level >1.0 ng/ml.

The number of intensive care days with an "alert procalcitonin" after the first "alert procalcitonin" (censored at death/discharge or 10 days) was equal (median, 1 day; interquartile range, 0–2 days in both arms). "Alert procalcitonin" at baseline was an independent predictor of 28-day all-cause mortality (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1–1.9) in a model including eight other known and suspected predictors of mortality. In a logistic regression model, the risk of having severe sepsis or septic shock on day 5 increased with the number of "alert procalcitonin" within the first 5 days (OR no "alert procalcitonin," 1.0 [reference]; one "alert procalcitonin," 2.2; 95% CI, 1.2–4.1; two or more "alert procalcitonin," 3.0; 95% CI, 1.9–4.8).

Algorithm Adherence and Use of Antimicrobial Interventions

Adherence to the Procalcitonin Algorithm. In the procalcitonin group, 256 of 312 (82.1%) of patients with baseline "alert procalcitonin" received antimicrobials according to the available procalcitonin measurement and the intervention algorithm and 292 of 312 (93.6%) received any β-lactam therapy as part of either procalcitonin-guided intervention or standard of care (the protocol specified that verified microbiologic etiology should result in specific antimicrobial therapy).

Adherence to Standard-of-Care Guidelines. Of patients in the standard-of-care-only arm, who were judged to have severe sepsis or septic shock at baseline, 172 of 209 (82.4%) received antimicrobials according to empiric "standard-of-care" principles, and 196 of 209 (93.8%) received any β-lactam therapy either as an empiric therapy or as a specific therapy based on verified microbiologic etiology.

Antimicrobial Interventions

The use of antimicrobial therapy was substantially increased in the procalcitonin

Table 2. Consumption of antimicrobials during follow-up

Consumption of Antimicrobials	Standard-of-Care-Only (n = 596)	Procalcitonin-Guided (n = 604)	*p*
Piperacillin/tazobactam used within 28 days (DDD)	1893	2925	—
Proportion of days[a] followed when piperacillin/tazobactam was used	0.00 (0.00–0.33)	0.11 (0.00–0.56)	<.001
Meropenem used within 28 days (DDD)	2174	2480	—
Proportion of days[a] followed when meropenem was used	0.00 (0.00–0.00)	0.00 (0.00–0.07)	.23
Cefuroxime used within 28 days (DDD)	4369	3390	—
Proportion of days[a] followed when cefuroxime was used	0.11 (0.00–0.39)	0.04 (0.00–0.29)	<.001
Ciprofloxacin used within 28 days (DDD)	6210	8382	—
Proportion of days[a] followed when ciprofloxacin was used	0.21 (0.00–0.71)	0.33 (0.04–0.88)	<.001
Number (%) intensive care unit days spent with at least three antimicrobials	2721 (57.7%)	3570 (65.5%)	.002

DDD, defined daily dose administered within 1–28 days.

[a]This comparison was made with complete follow-up for 28 days (if patients were discharged from the intensive care unit, they were followed for antimicrobial use in all hospital admissions in Denmark).

group during follow-up, as intended in the design of the study, especially regarding broad-spectrum antimicrobials like piperacillin/tazobactam and meropenem (Table 2). The median length of an antibiotic course (while in the intensive care unit) was prolonged using the procalcitonin algorithm (6 days [interquartile range, 3–11] vs. 4 days [interquartile range, 3–10]), and the time to administration of vancomycin or fluconazole was shorter in the procalcitonin-guided patients with a secondary "alert procalcitonin" (adjusted for day of recruitment: hazard ratio, 1.8; 95% CI, 1.3–2.4, for procalcitonin vs. standard-of-care-only). The time to appropriate antimicrobial was administered was not different between the groups, except for patients who had bacteremia (Table 3).

Patients in the procalcitonin group were more likely to have additional cultures performed within 24 hrs after an "alert procalcitonin" than patients in the standard-of-care-only group: 81.5% vs. 66.7% ($p < .001$) but no more likely to have imaging studies or surgical interventions (data not shown).

28-Day Survival: Primary End Point

Twenty-eight days after enrollment, 190 participants in the procalcitonin group and 191 participants in the standard-of-care-only group had died. The time to death was comparable between the two treatment groups (Fig. 3). The absolute risk reduction (procalcitonin vs. standard-of-care-only) was 0.6% (95% CI, −4.7 to 5.9) and the relative risk was 0.98 (95% CI, 0.83–1.16; $p = .83$). We examined the robustness of the primary end point analysis in the seven predefined subgroups and these results are consistent with the overall result and no interaction was observed (Fig. 4). A *post hoc* subgroup analysis of the patients with "alert procalcitonin" at any time vs. patients with "nonalert procalcitonin" additionally did not reveal any difference and there was no interaction between these groups (data not shown).

Secondary Outcomes

In the procalcitonin and in the standard-of-care-only groups, a total of 3,569 days (65.5%) and 2,861 days (60.7%) ($p < .001$) were spent on mechanical ventilation, respectively (Table 4). Additionally, the median intensive care unit admission length was longer in the procalcitonin vs. the standard-of-care-only group (6 [3–12] vs. 5 days [3–11], $p = .004$).

In 1162 episodes of microbiologically verified nonbloodstream infection, the mean time to appropriate antimicrobials was 0.2 days vs. 0.4 days (procalcitonin group vs. standard-of-care-only group) ($p = .61$). In 179 patients with bacteremia/fungemia (excluding coagulase-negative staphylococci, corynebacteria, propionibacteria, and only including the first episode), a shorter time to administration of appropriate antimicrobials was observed for the procalcitonin group as compared with the standard-of-care-only group: −0.1 days vs. 0.8 days ($p = .02$), counting from the time of culture sampling (Table 3). For patients with nonbloodstream infections identified microbiologically, the time to appropriate antimicrobial therapy was similar.

The rate of infection at the time of discharge or at day 28 among the 819 patients who were still alive was 69.6% in both treatment arms (Table 4) and no difference was found in the frequency of any organ failure measure on the day of discharge between the two groups. At 60 days follow-up, 231 (38.2%) vs. 220 (36.9%) had died.

A total of 14,515 unique cultures were performed on days 1–28 (excluding multiple cultures from the same site and date), 7874 in the procalcitonin group and 6641 in the standard-of-care-only group. Of these, 1,852 vs. 1,550 blood cultures, 2,258 vs. 1,947 airway cultures, 1,630 vs. 1,332 urine cultures, and 376 vs. 321 intraabdominal samples were performed and in the remaining sample categories, 1,758 vs. 1,491 samples were performed. Gram-negative rods other than wild-type *E. coli*/*Klebsiella* (more resistant strains) were identified in 187 of 7,874 samples in the procalcitonin group (2.4%) vs. 204 of 6,641 samples (3.1%) in the standard-of-care only group ($p = .01$). The frequency of fungi cultured was 688 of 7,874 samples (8.7%) vs. 584 of 6,641 samples (8.8%) ($p = .91$).

DISCUSSION

Our data show that clinician knowledge of procalcitonin levels in real time, 365 days/yr, together with a proactive intervention algorithm consisting of diagnostic and therapeutic antimicrobial actions did not improve survival and did worsen other patient outcome parameters and resulted in a prolonged length of stay in the intensive care unit compared with patients receiving standard of care in Danish intensive care units. Despite leading to substantially higher use of broad-spectrum antimicrobials, especially piperacillin/tazobactam and ciprofloxacin, the procalcitonin-guided strategy did not lead to earlier appropriate

Table 3. Time to administration of appropriate antimicrobials

Site of Infection	Standard-of-Care-Only No.[b]	Standard-of-Care-Only Days, Median (Interquartile Range)	Standard-of-Care-Only Days, Mean (95% Confidence Interval)	Procalcitonin-Guided No.[b]	Procalcitonin-Guided Days, Median (Interquartile Range)	Procalcitonin-Guided Days, Mean (95% Confidence Interval)	p^a
Blood[c]	82	0 (−1 to 1)	0.8 (0.0 to 1.6)	97	0 (−1 to 0)	−0.1 (−0.5 to 0.2)	.02
Abdomen	61	0 (−3 to 1)	−1.1 (−2.5 to 0.3)	46	0 (−4 to 1)	−2.3 (−4.7 to 0.0)	.83
Soft tissue, bonen and joint	10	0 (−1 to 0)	−0.2 (−4.8 to 4.4)	9	0 (0 to 1)	1.2 (−0.5 to 3.0)	.15
Respiratory tract	304	1 (0 to 2)	0.5 (−0.2 to 1.1)	362	0 (0 to 2)	0.5 (−0.1 to 1.1)	.72
Urinary tract	82	1 (0 to 4)	1.6 (0.0 to 3.2)	93	0 (0 to 2)	0.4 (−0.8 to 1.5)	.15
Catheter	8	1 (−1 to 3.5)	0.5 (−2.9 to 3.9)	9	0 (0 to 7)	1.0 (−4.1 to 6.1)	.96
Other/unknown	35	−1 (−3 to 0)	−1.1 (−3.2 to 1.0)	45	0 (−2 to 1)	−0.8 (−2.7 to 1.0)	.36
All nonblood sites	552	0 (0 to 2)	0.4 (−0.1 to 0.9)	610	0 (−1 to 2	0.2 (−0.3 to 0.6)	.61

[a]*p* value is based on nonparametric statistics, but no *p* values changed from significant to nonsignificant or vice versa when comparing means in Student's *t* test; [b]samples from nonblood sites: in patients with several different micro-organisms cultured, time to appropriate antimicrobials has been analyzed for all micro-organisms and in cases with more than one episode with the same micro-organism, only the first episode was analysed; [c]blood culture: in patients with more than one episode of positive blood culture, only the first episode was analyzed.

Based on patients with positive cultures. Appropriate antimicrobial therapy was considered to be antimicrobials with *in vitro* activity appropriate for the isolated pathogen or pathogens. Time in days to appropriate antimicrobials have been administered is counted from the time of sampling, i.e., negative time represents antimicrobials being administered before the sampling time. Cultures with coagulase negative staphylococci, corynebacteria, and propionibacteria are not included.

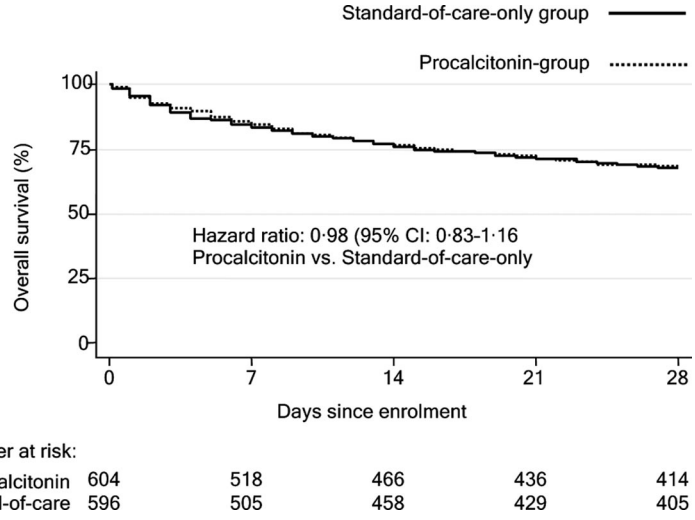

Figure 3. Kaplan-Meier estimates of 28-day survival. The analysis is based on the intention-to-treat population. The log-rank test *p* value was.80. The overall nonadjusted hazard ratio is displayed. Subgroup analysis of seven predefined subgroup separators was made (described in "Results" section). *CI*, confidence interval.

antimicrobials, except in the subgroup of patients with verified bloodstream infections. Because early appropriate antimicrobials are solidly documented to lead to improved prognosis (4, 6), the failure to achieve this generally in patients with infections using the procalcitonin strategy may be the main reason the strategy did not succeed.

The prespecified subgroup analyses revealed that the procalcitonin strategy did not have an effect on the primary outcome in any subgroup of patients and the interaction tests were negative. A supplementary nonprespecified subgroup analysis only including the patients who at any time had an "alert procalcitonin" was also negative regarding the primary end point. Procalcitonin daily changes, i.e., "alert procalcitonin" as a predictor of mortality, as earlier observed (23), was confirmed. The risk of persistent or progressing infection (having severe sepsis/septic shock) on day 5 increased as expected with the number of "alert procalcitonin" within the first 5 days confirming the results regarding treatment failure and procalcitonin day-to-day changes found in other studies (27, 28).

The secondary end point analyses revealed that patients in the procalcitonin group needed mechanical ventilation for substantially longer and likewise had a low estimated glomerular filtration rate for more days and needed dialysis for a longer time. Additionally, there was a tendency toward need for vasopressor/inotropic therapy for a longer time and a longer period with severe sepsis/septic shock. In addition to this, the length of stay in the intensive care unit was prolonged using the procalcitonin strategy. All these measures suggest a harm effect from the procalcitonin strategy. Because harm from blood sampling can be ruled out (both groups had daily study blood samples), only diagnostic procedures and high exposure to broad-spectrum antimicrobials can be the explanation. Regarding diagnostic procedures, radiology was not performed more often using the procalcitonin strategy; however, the frequency of microbiologic sampling was increased, mainly attributed to more airway samples, urine samples, and blood cultures. These culture sample procedures are, in nearly all instances, minimally invasive and are not causally linked to adverse outcome, so this does not seem to explain the rather pronounced harm effects observed, leaving high exposure to broad-spectrum antibiotics as the most likely explanation. So, what could be the mechanism for this harm of broad-spectrum antimicrobials used?

First, broad-spectrum antimicrobials may have led to selection of micro-organisms resistant to different antimicrobials, which then could have led to treatment-resistant nosocomial infections and fungal infections. However, the

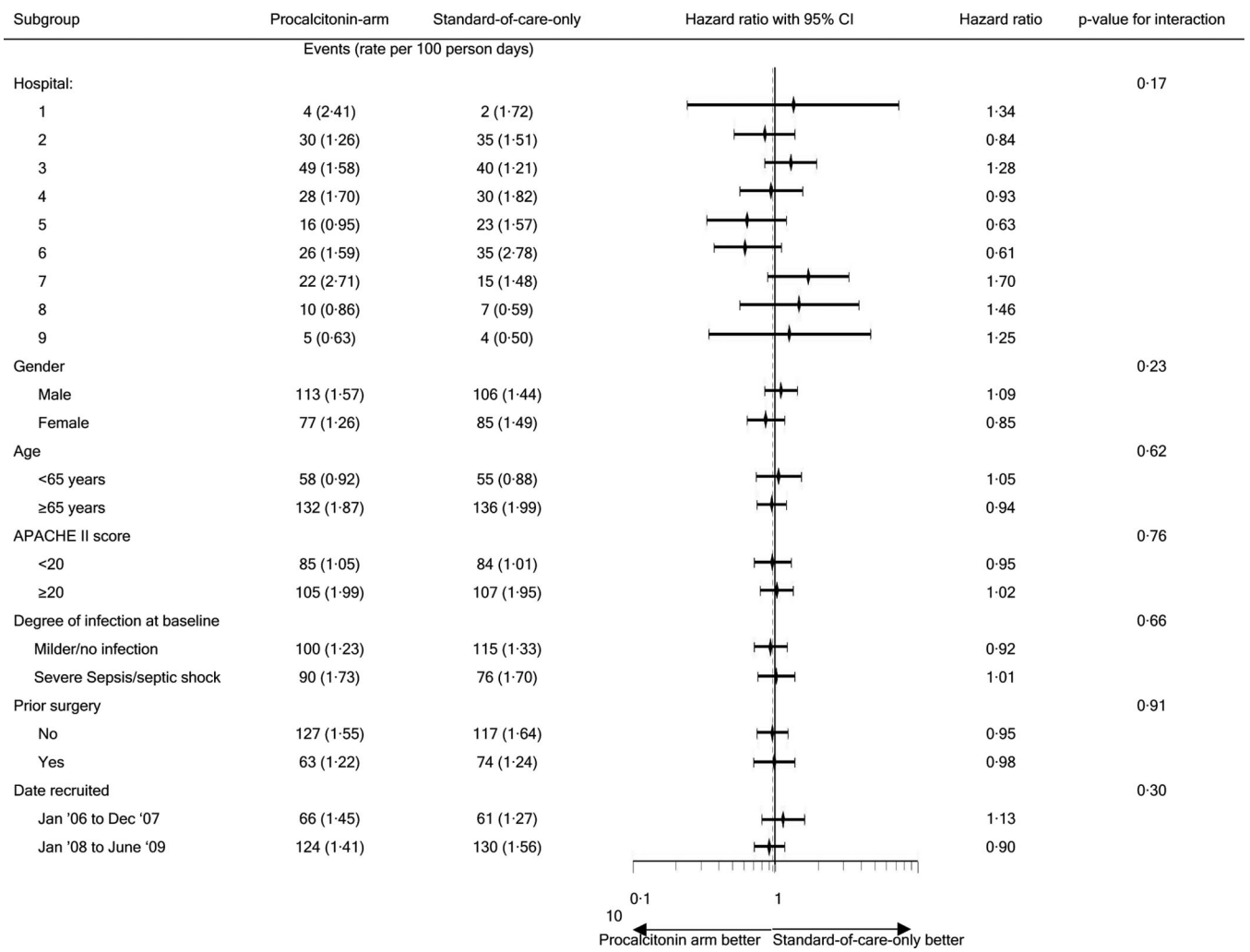

Figure 4. Subgroup analysis regarding 28-day all-cause mortality. Hazard ratios and 95% confidence intervals (*CIs*) for death in the 28 days after recruitment for the procalcitonin arm compared with the standard-of-care-only arm. This figure shows the overall nonadjusted hazard ratio in a dashed line: 0.98 (95% CI, 0.80– 1.19, procalcitonin vs. standard-of-care-only groups) and the hazard ratios for each of the seven predefined subgroups. All subgroups include all 1200 persons and interaction test is negative for all subgroups. Acute Physiology and Chronic Health Evaluation II Score (*APACHE II*) ranges from 0 to 71, and high scores indicate less favorable prognoses.

frequency of cultures with Gram-negative rods other than wild-type *E. coli/Klebsiella* and of fungi was, in fact, lower in the procalcitonin group, and the rate of fungal infections was comparable. Second, a toxic effect on renal tissue and respiratory tissue from the drugs used in the intervention algorithm, or combinations of them, may have induced the observed prolongation of organ failure in these vulnerable patients. Clinical harm effects of high exposure to broad-spectrum antimicrobials have been shown in other studies in this setting (29). Of note, several experimental studies with healthy humans have demonstrated a reversible renal function decrease on administration of piperacillin (30, 31), and a competitive inhibition of renal tubular secretion has been identified as the pathophysiological mechanism for this (32).

Interestingly, the sensitivity of the procalcitonin test for infection estimated in this trial was as low as 59%, which stresses the importance of not relying on the test for diagnosis of infection in these severely ill patients and likewise does underline the need for adherence to the current standard-of-care guidelines as used in both arms of this trial. In this context, it should be noted that another trial testing procalcitonin-guided therapy in critically ill patients recently observed an increase in organ failure in the last part of the observed period and a concerning tendency toward higher 60-day mortality (17). Large trials are right now ongoing to determine the safety of antibiotic-sparing procalcitonin strategies in intensive care (33, 34).

In the present trial, the procalcitonin strategy increased costs substantially, mainly on the following points: procalcitonin bioanalysis, additional use of broad-spectrum antibiotics, additional culture samples, more days using mechanical ventilation and dialysis, and a longer stay in the intensive care unit.

Our patients were critically ill, had a wide range of infections, had a high level of chronic diseases, two-thirds needed mechanical ventilation, and more than half had vasopressors/inotropics administered at baseline. Additionally, the sample size was high, only few exclusions were made, and complete follow-up for the primary end point was made possible by the Danish National Patient Register.

Several limitations to our study should be noted. First, although the PASS trial was multicentered and randomized, it was

Table 4. Organ failure and infection during follow-up

	Standard-of-Care-Only (n = 596)	Procalcitonin-Guided (n = 604)	Absolute Difference (95% Confidence Interval, Standard-of-Care Only vs. Procalcitonin-Guided)	p
Need for organ support, no. (%)				
ICU days[a] with mechanical ventilation	2861 (60.7)	3569 (65.5)	−4.9% (−6.7% to −3.0%)	<.0001
Mechanical ventilation on last ICU day (1200 days followed)	196 (32.9)	196 (32.5)	0.4% (−4.9% to 5.7%)	.87
ICU days[a] with vasopressors/inotropics	1393 (29.5)	1564 (28.7)	0.8% (−1.0% to 2.6%)	.86[b]
Patients with vasopressors/inotropics at discharge/death (1200 days followed)	122 (20.5)	113 (18.7)	1.8% (−2.7% to 6.3%)	.44
ICU days[a] with estimated glomerular filtration rate <60 mL/1.73 m^2	2187 (46.4)	2796 (51.3)	−5.0% (−6.9% to −3.0%)	.33[c]
Patients with estimated glomerular filtration rate <60 mL/1.73 m^2 at discharge/death	256 (43.0)	278 (46.0)	−3.1% (−8.7% to 2.5%)	.28
ICU days[a] spent with dialysis treatment	982 (20.8)	1214 (22.3)	−1.5% (−3.1% to 0.1%)	.31[d]
Patients in treatment with dialysis at discharge/death	86 (14.4)	84 (13.9)	0.5% (−3.4% to 4.5%)	.80
Other organ failure measures, no. (%)				
ICU days[a] with bilirubin >1.2 mg/dL	900 (19.1)	809 (14.9)	4.2% (2.8% to 5.7%)	.83[e]
Patients with bilirubin >1.2 mg/dL at discharge/death	82 (13.8)	76 (12.6)	1.2% (−2.7% to 5.0%)	.55
ICU days[a] spent with Glasgow Coma Score ≤13	387 (8.2)	361 (6.6)	1.6% (0.6% to 2.6%)	.52[f]
Patients with Glasgow Coma Score ≤13 at discharge/death	50 (8.4)	61 (10.1)	−1.7% (−5.0% to 1.6%)	.31
Infection/host response by clinical assessment[h], no. (%)				
ICU days[a] with severe sepsis/septic shock	924 (19.6)	1097 (20.1)	−0.6% (−2.1% to 1.0%)	.33[g]
ICU survivors with infection clinically judged[h] at the time of discharge (n = 819)	282 (69.6)	288 (69.6)	−0.1% (−6.2% to 6.4%)	.98

ICU, intensive care unit.

[a]Estimates and statistics were made as "fraction of days followed in the intensive care unit" and percentages are calculated from the actual time in the ICU. Because the ICU length of stay was increased in the procalcitonin group, statistics may underestimate the differences. The data for these analyses were from the recruiting ICU site. Of all admissions to ICUs, this corresponds to a follow-up of: (procalcitonin group vs. standard-of-care-only): 5,447 of 5,700 days (95.6%) vs. 4,717 of 5,194 days (90.8%) according to the nationwide Danish National Patient Register. Follow-up was 11,380 days (procalcitonin group) and 10,755 days (standard-of-care-only group). If defining follow-up as "all admitted days in hospitals," within 28 days, comparisons were as follows: [b]$p = .09$, [c]$p < .0001$, [d]$p = .0001$, [e]$p = .0005$, [f]$p = .09$, [g]$p = .007$, [h]"infection" (19).

mononational with the inborn limitations of this such as a low microbial resistance rate and a corresponding restrictive antibiotics policy. Second, although most patients were clinically rated as having severe infections and corresponding host response, far from all patients had bloodstream infections, which are the most potent stimulus of procalcitonin increases, which in our trial according to the hypothesis would initiate interventions before the culture sample was reported. The inclusion criteria allowed for noninfected patients to be recruited. This was decided in the steering committee, because we judged that infections acquired during the intensive care admission should be a target for the procalcitonin strategy. Third, the adherence to the algorithm was not complete for patients with "alert procalcitonin" at baseline, and although 94% did receive β-lactam therapy with spectrum-like ceftriaxone or broader either as part of the procalcitonin algorithm or as standard-of-care therapy in the procalcitonin group, the remaining patients may have been undertreated. However, standard-of-care guideline adherence in the standard-of-care-only group was comparable. Fourth, the cutoff level for interventions of 1.0 ng/mL (with a corresponding sensitivity for infection–host response of 59%) may have reduced the frequency of potential interventions in patients with early-phase infections. When PASS was designed, previous studies had suggested an optimal cutoff for determining sepsis in intensive care unit patients of 1.0 ng/mL (35). This cutoff had additionally been suggested to predict mortality, and noninfectious causes of procalcitonin increase would not normally lead to procalcitonin above this (23, 36). The dynamic (day-to-day procalcitonin change) part of the definition of "alert procalcitonin" was supported by observations of kidney function and procalcitonin and dialysis (37–40). Several studies have documented that when progressing infection is not being treated adequately, procalcitonin levels are substantially altered at admission (41) and do not decrease within 24 hrs (42).

CONCLUSION

A strategy with escalation of broad-spectrum antimicrobials in the intensive care unit guided by daily procalcitonin measurements as used in this trial did not improve survival and did lead to an increased use of broad-spectrum antimicrobials, which is concerning in regard to toxicity, resistance, and economics. We observed deleterious effects on organ function and length of stay in the intensive care unit and the strategy cannot be recommended.

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